REMARKS

Paragraph 77 has been amended to correct an obvious error. Since "Example 1" is the example of which paragraph 77 is a part, and no description of observation and recordation is included in Example 1, paragraph 77 must refer to the previous description in Preparation A. No new matter is added by this correction.

Claim 2 has been amended simply to provide antecedent basis for "said first and second fluorophores" in claim 3. Clearly this raises no new issues, as the amendment is in direct response to a rejection made for the first time in this Office action. Therefore, applicants respectfully request that the Examiner exercise her discretion and enter this amendment.

The invention provides a simple and direct method to identify a region of a target nucleic acid to be targeted for observation by bracketing the desired sequence using microscopically observable particulate labels that permit detection in the presence of irrelevant nucleic acids and without the necessity for the removal of unbound labels from the sample. In addition, because two independent binding events are required to generate the signal of interest, the noise is greatly reduced, roughly by the square root. This offers an advantage over the method of use described, for example, by Barbera-Guillem, of microspheres in general and obviates any need to amplify the nucleic acids tested or to chemically modify them in any manner other than fragmentation. Respectfully, the cited art does not suggest this invention.

The rejections of record are addressed as follows:

The Rejection of Claims 1-16 Under 35 U.S.C. § 112, First Paragraph

The basis for this rejection is asserted failure of the claims to comply with the written description requirement based on what the Office sees as new matter. The objected to phrase is

"wherein said method does not include a step of separating the target nucleic acid from non-target nucleic acid."

First, it is apparent from the procedure in Example 1, for example, that no separation of target nucleic acid from non-target nucleic acid is required. Total genomic DNA is employed in the assay. There should be no need for applicants to specifically state all the steps that are not taken – *e.g.*, the sample is not heated, not subjected to pressure, not distilled, etc. If there is no separation described, it should be apparent that none is required.

Second, there is explicit support in the specification. The Office questions the support on page 7, in the first line of paragraph 26, which states that "The present invention offers highly sensitive ways to analyze a target nucleic acid without the need for physical separation steps." The Office states that this could mean that the invention does not require the step of separating the target from non-target or could mean that the invention does not require the step of separating unbound probes.

Applicants believe the statement is clear. It means that no separation steps are required, period. Neither the step of separating target nucleic acid nor the step of separating unbound probes prior to detection is required. If there were any doubt of this, it is confirmed by Example 1 which employs genomic DNA without further purification and the mixture of nucleic acids is observed and recorded as described in Preparation A. In that preparation, both bound and unbound probes are observed.

Thus, there is both exemplification of a lack of separation of target from non-target nucleic acid and an explicit statement that none is required.

The Rejections Under 35 U.S.C. § 112, Paragraph 2

The Office objects to the phrase "observing by microscopy the presence or absence of proximity" in claims 1 and 8. The Office appears to consider it necessary to require a specified number of nucleotides in the intervening sequence in order to define what is meant by "proximity." Respectfully, applicants believe this is unnecessary, as this phrase would be clearly understood by those skilled in the art. The nature of the observation is perhaps best made clear on page 22, in paragraph 73. Essentially what is observed are "red/green pairs" or pairs of any color or colors. The presence of two labels as a "pair" would be readily distinguishable from isolated occurrences of the label. There would be no doubt in the mind of the skilled artisan which beads were paired and which were not.

The Office further objects to the phrase "whereby the presence of said proximity identifies said desired region." This seems to be another aspect of the same problem – if a "pair" is identified, this indicates the desired region to be probed as explained in the specification. This is because one member of each pair will be at either side of the region.

Claim 2 has been amended to provide antecedent basis for "said first and second fluorophores" in claim 3. It is believed that the corresponding phrase in claim 9 is already supported by antecedent basis in present claim 8.

In view of the foregoing amendments and explanations, applicants believe that the rejections under 35 U.S.C. § 112, first and second paragraphs, may be withdrawn.

The Rejections Under 35 U.S.C. § 103

Claims 1-3, 5, 7-10, 12, 14-15 and 17 were rejected under this section of the statute as assertedly obvious over Gray, *et al.* (US 6,475,720) in view of Barbera-Guillem, *et al.*

(US 6,309,701). Essentially, the basis for rejection is that it would have been obvious to substitute the particulate labels of Barbera-Guillem (coupled to oligomers) as probes in place of the assertedly less intense labels employed in the detection of a fused chromosome in a procedure described beginning in column 58 of Gray, at line 55. Applicants believe the combination of these documents is not suggested by the art, but by the invention itself, that no motivation can be found to combine these documents, and that even if combined they fail to suggest the invention as claimed.

The requisites for justifying a rejection based on a combination of documents are clearly set forth by the Federal Circuit in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998). First, this case clearly holds that in order for patentability to be defeated, a rationale for combining the documents, absent the teaching of the invention, must be articulated. The Office states that Barbera-Guillem teach several advantages of using particulate labels over conventional fluorescent labels to detect nucleic acid hybridization. Applicants are unable to find such a teaching in Barbera-Guillem. It is true that Barbera-Guillem teach that their particular microspheres have a far greater degree of fluorescence intensity (intensity) than previously known fluorescent microspheres and that they may be used for measuring a plurality of analytes in a single sample (column 2, lines 30-35). (According to the Office, they are also said to be resistant to photo-bleaching, although the location of this statement is not readily apparent to applicants.) Nowhere, however, does Barbera-Guillem teach advantages of using these labels "to detect nucleic acid hybridization." Thus, this guidepost reflecting the advantages is missing from the document cited. The only mention of nucleic acids applicants are able to find is an incidental mention of single-stranded RNA or single-stranded DNA or single-stranded nucleic acid hybrids in column 3, at line 55, on a laundry list of possible affinity ligands. There is no reason to select these embodiments over the others in the list. Thus, it is

simply not true that Barbera-Guillem teach particular advantages to "detect nucleic acid hybridization" *per se*.

And, there is no suggestion in Gray that anything other than the labels specified there, be used. There is no suggestion that the procedure that is disclosed, beginning at the bottom of column 58, needs to employ any labels other than those actually used. Nor would Gray have any motivation to do so since detection of a fused chromosome by staining flanking regions from the two parental chromosomes affords an effectively unlimited amount of DNA on each flank allowing a very bright signal to be generated by conventional staining of the considerable DNA on each flank. Detection of fragmented DNA in solution is quite a different matter, with analyte sizes ranging from 10 to 100,000 base pairs.

Thus, neither document makes the suggestion that it should be combined with any other.

This is significant because the holding in *Rouffet* recognizes only three acceptable motivations to combine documents, and the first of these is a suggestion in one or both of the documents themselves. This criterion is not met.

A second acceptable basis for motivation is the nature of the problem to be solved. That is, the combination of the documents solves a problem that is addressed by the invention, or one document solves a problem that is posed by the other. The problem solved by the invention is to identify a portion of a nucleic acid that can be further interrogated to discern its nature. As noted above, this is only tangentially related to the problem solved by the cited portion of Gray – *i.e.*, to identify the presence of a fused DNA, and unrelated to any problem to be solved by Barbera-Guillem. The problem to be solved by that disclosure is to provide brighter microspheres. Thus, neither document solves any problem addressed by the invention, nor does either document

solve a problem defined by the other. Accordingly, the second criterion recognized by *Rouffet* is not met.

The third criterion that is acceptable is the circumstance under which one of the documents is of such high profile that it would be immediately in the mind of the skilled practitioner – such as, for example, the Kohler-Milstein paper on preparation of monoclonal antibodies. There is no question that that is not the case here.

Respectfully, applicants believe that only the teachings of the invention have been used to combine the assembled documents and that on this basis alone the rejection should be withdrawn.

This conclusion is reinforced by the background fact that there are many disclosures of particulate labels *per se* that could be used in the method of the present invention. In order to render the present invention obvious, however, either the disclosures of these particulate labels would need to suggest something other than assays which employ only a single label, such as those in examples 3-6 of Barbera-Guillem where only a single analyte binding to a single bead is detected, or the disclosure of Gray would need to indicate that there was something wrong with the labels employed. Neither is the case.

Further, even if combined, the documents do not suggest the invention. The holding in *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992) is controlling. The present invention is a selection invention wherein the particulate labels of Barbera-Guillem (or of any of a number of other documents) are commandeered specifically for a particular purpose putatively disclosed by Gray. *Jones* also concerns a selection invention.

In *Jones*, the claims were directed to a particular salt of a known acid, dicamba. Both the claimed 2-(2′-aminoethoxy)ethanol salt and the known dicamba and its salts in general were said to

be herbicides. Dicamba and its salts in general were disclosed in a document used as a primary reference. The PTO combined this disclosure (which included disclosure of the ammonium salts of dicamba, a genus of which the claimed salt was a species, as well as several examples of such salts) with a secondary document describing the specific amine compound used to make this salt. The PTO argued that it would be obvious to substitute the amine of the secondary reference for the specific amines exemplified in the primary reference to result in the claimed salt. The Court reversed and cited *In re Fine*, 837 F2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Lalu*, 747 F2d 703, 223 USPQ 1257 (Fed. Cir. 1984) for the principle that in order for the combination of these documents (said combination having already been made) to suggest the claimed salt, such a substitution must either be suggested by the documents themselves or by the knowledge of the art.

The Office has pointed to nothing in the cited art or in the general knowledge of the art that would suggest substituting the microspheres of Barbera-Guillem for the labels used in the assay taught by Gray. There is certainly nothing in Gray that would point one to any similarity of the labels actually used to the microspheres, just as there was nothing in the primary document in *Jones* to suggest that the specific amine of the secondary reference should be substituted for the specifically named amines it disclosed, or to suggest its use as a representative of the genus the primary document disclosed.

So, as in *Jones*, the combination of Gray and Barbera-Guillem, even if made, does not suggest the invention.

A third reason that the cited documents do not defeat patentability is that the preamble of the claim is significant in this case. The claim is directed to a method to "identify a desired region of a target nucleic acid to be targeted for observation." As has been held previously, if the preamble

results in a limitation on the remainder of the claim, the preamble needs to be considered as limiting the scope of the claim. This is exemplified, for example, in the holding in *Corning Glass Works v. Sumitomo Electric U.S.A., Inc.*, 868 F2d 1251, 9 USPQ2d 1962 (Fed. Cir. 1989), where a preamble that indicated the recited components were components of a waveguide distinguished the subject matter from a prior art apparatus that contained the actively recited components, but was not a waveguide. The Court considered that the requirement that the apparatus be a waveguide imposed certain limitations on these components that would not be found in the prior art.

The point made in *Corning* was reaffirmed in the more recent decision *Poly-America LP v. GSE Lining Tech., Inc.*, 383 F3 1303, 72 USPQ2d 1685 (Fed. Cir. 2004).

In *Poly-America*, a preamble that characterized the recited features listed in the body of the claim as composing a "blown film" was construed as a substantive limitation. The claim recited three different layers of thermoplastic materials, which, if taken alone, apparently described material that was in the prior art. However, with the inclusion of a "blown film" as a limitation, the prior art was considered avoided. This sufficiently avoided the prior art that the Federal Circuit refused to reverse the District Court's denial of GSE's Motion for JMOL of invalidity. The Court came to this conclusion on the basis that their analysis of the application "shows that the inventor considered that the 'blown film' preamble language represented an important characteristic of the claimed invention." Clearly the preamble here states an important characteristic of the present invention as it is the entire purpose thereof.

And also, here, the preamble imposes limitations on the method steps because the nature of the substrate that would be used in the assay set forth in the body of the claim is limited thereby.

The substrate would be different from the substrate used in Gray, since Gray had no interest in ascertaining any targeted region to be further interrogated.

As dictated by the holdings in *Rouffet*, *Jones*, and *Corning*, it is respectfully submitted that this basis for rejection may be withdrawn.

Claims 4, 6, 11 and 13 were rejected as assertedly obvious over the combination of Gray and Barbera-Guillem in further view of Nie (US 6,060,242).

These claims add the further limitations that the oligomers are peptide nucleic acids or that triplexes are formed. Nie is said to teach these possibilities.

However, Nie teaches these matters in an entirely different context, and there is no more motivation to combine Nie with the remaining references as there is to combine Gray with Barbera-Guillem.

Claim 16 was rejected over Gray in view of Barbera-Guillem and in further view of Ward (US 6,506,563). Claim 16 requires that the organism from which the nucleic acid is derived is an infectious agent. The Ward document fails to teach probes capable of binding chromosomes, including those of bacteria or viruses in any context that would motivate the combination of Ward with the remaining documents. For this reason, the rejection of claim 16 may also be withdrawn.

Conclusion

In view of the lack of motivation to combine Gray with Barbera-Guillem (*Rouffet*), or to select the particular affinity ligand described in Barbera-Guillem for its particles to conduct the method described by Gray (*Jones*), and in view of the relevance of the preamble of claim 1 (*Corning*), applicants respectfully submit that the pending claims 1-17 are not made obvious by the

art Accordingly, applicants believe claims 1-17 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512011000.

Respectfully submitted,

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